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***Abstract*—In molecular communication systems operating in a crowded biochemical environment, there is the potential for unintended chemical or physical interactions with external biochemical systems. In order to avoid these interactions, or ensure *coexistence*, it is necessary to tailor the signaling scheme. In this paper, we propose a signaling strategy exploiting chemical reactions between different transmitted chemical species. While intuitively appealing, the non-linear nature of the governing partial differential equations (PDE) means that selecting the signaling strategy to minimize the probability of error is computationally challenging. To reduce this computational burden, we introduce a new proxy metric called the modified signal-to-interference difference ($mSID$). We show that optimizing the mSID yields low complexity and near-optimal solutions, requiring only deterministic nonlinear programming rather than standard brute force Monte Carlo methods.**

***Index Terms*—Molecular Communications, Coexistence, Reactive Signaling**

I. Introduction

Molecular communication—where information is encoded in the quantity, type or time of release of molecules—is increasingly expected to play an important role in the control of complex biochemical systems [1]. As such, the design of molecular communication systems must consider not only performance, but also the impact on external biochemical systems. This issue, called the *coexistence problem* in [2], [3] is an example of the difficulty of providing modularity in biological systems. Although such modularity has been widely studied within the system biology literature, there has only been limited attention to this issue focusing on molecular communications [4].

On the other hand, the design of efficient signaling strategies for molecular communications via diffusion has progressed rapidly. A particularly promising approach is to exploit a number of different molecules in order to reduce intersymbol interference, leading to molecular shift keying (MoSK) schemes [5], [6].

Very recently, reactive signaling exploiting multiple information-carrying molecules has been introduced in [7], [8]. In this work, information is carried by molecules of Type-A and another chemical species of Type-B is introduced to remove molecules of Type-A within the channel. This approach differs from [9] where secondary chemical species are introduced within the channel by an external mechanism.

An important feature of reactive signaling, unlike MoSK-type schemes which exploit processing only in the receiver [5], [6] is that it can play an important role in achieving coexistence. As signaling molecules of Type-A are removed *in the channel*, interactions with external biological systems can be reduced.

In this paper, we propose a reactive signaling scheme accounting both for the reliability of the communication system and coexistence with an external biological system. This is achieved by formulating a new optimization problem for the quantity of molecules of Type-B, as well as their time of release as previously proposed for a non-reactive scheme in [5]. In previous reactive signalling studies, ([7], [8]) the quantity of Type-B and release time of molecules were kept fixed, these two parameters may be adjusted to improve both the performance of reactive signaling satisfy the coexistence constraint.

Moreover, a key difficulty in obtaining optimal reactive signaling schemes is estimating the probability of error. In [7], [8], this was achieved via extensive Monte Carlo simulations. In order to avoid Monte Carlo simulations, we propose a new alternative metric, *modified signal-to-interference difference (mSID)*. With the aid of the mSID, the quantity of released molecules and the time of release can also be obtained via the numerical solution of reaction-diffusion equations. We show that the mSID objective significantly reduces the computation time, while yielding a nearly optimal probability of error.

II. System Model

Consider a point transmitter (Tx) that sends a sequence of binary messages $s[k] \in \{0,1\},\ k = 0,1,\ldots,K-1$ to a passive spherical receiver (Rx) with radius r at a distance d from the transmitter. The sequence $s[k] = 0,\ k = 0,1,\ldots,K-1$ is denoted by $\mathbf{s}_0$.

In the transmission of each binary message $s[k]$ two types of molecules are sent, denoted by Type-A and Type-B, respectively. Let $N_{\mathsf{A}}[k]$ denote the maximum number of molecules of Type-A released at the beginning of time slot k, $N_{\mathsf{B}}[k]$ be the maximum number of molecules of Type-B released in time slot k, and τ denote the time of release of the Type-B molecules. The molecules released in time slot k can therefore be parameterized by $(N_{\mathsf{A}}[k], N_{\mathsf{B}}[k])$. We consider the scheme

$$(N_{\mathsf{A}}[k], N_{\mathsf{B}}[k]) = \left\{ \begin{array}{ll} (N_{\mathsf{A}}, N_{\mathsf{B}}) & s[k] = 1 \\ (0,0) & s[k] = 0. \end{array} \right\} \quad (1)$$

For a symbol duration of t_s seconds, the set of potential release times for molecules of Type-A and Type-B, respectively, are

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given by

$$\begin{aligned}\mathcal{T}_{\mathsf{A}} &= \{t : t = kt_s,\ k = 0, 1, \ldots,\ \text{such that } s[k] = 1\} \\ \mathcal{T}_{\mathsf{B}} &= \{t : t = kt_s + \tau,\ k = 0, 1, \ldots,\ \text{such that } s[k] = 1\}.\end{aligned} \tag{2}$$

A key motivation for the introduction of Type-B molecules is to reduce intersymbol interference via chemical reactions. As such, we assume that

$$\mathsf{A} + \mathsf{B} \xrightarrow{\kappa} \emptyset, \tag{3}$$

where $\emptyset$ denotes any species that does not interact with the molecular communication system or its environment and κ represents the reaction rate.

Largely due to the difficulty of appropriately modeling the conditions under which a reaction will occur, there are three popular stochastic models for mesoscale reaction-diffusion systems; namely the Doi, Smoluchowski, and the reaction-diffusion master equation [10]. However, even restricted only to unimolecular and biomolecular reactions, these models have limited tractability. An alternative is to exploit a simplified model, where the quantity of molecules in a given domain at a given time is Poisson distributed. In particular, the number of molecules in the receiver at time t satisfies

$$y_i \sim \mathrm{Poi}(\overline{y}_i(t)),\ i \in \{\mathsf{A}, \mathsf{B}\}, \tag{4}$$

where

$$\overline{y}_i(t) = \int_{r \in \mathcal{V}^{\mathrm{Rx}}} C_i(\mathbf{x}, t)\mathrm{d}\mathbf{x},\ i \in \{\mathsf{A}, \mathsf{B}\} \tag{5}$$

with $\mathcal{V}^{\mathrm{Rx}}$ denoting the domain defining the receiver and $C_i,\ i \in \{\mathsf{A}, \mathsf{B}\}$ is defined by the reaction-diffusion equations

$$\begin{aligned}\frac{\partial C_{\mathsf{A}}(\mathbf{x}, t)}{\partial t} &= D_{\mathsf{A}}\nabla^2 C_{\mathsf{A}}(\mathbf{x}, t) - \kappa C_{\mathsf{A}}(\mathbf{x}, t)C_{\mathsf{B}}(\mathbf{x}, t) + G_{\mathsf{A}}(\mathbf{x}, t) \\ \frac{\partial C_{\mathsf{B}}(\mathbf{x}, t)}{\partial t} &= D_{\mathsf{B}}\nabla^2 C_{\mathsf{B}}(\mathbf{x}, t) - \kappa C_{\mathsf{A}}(\mathbf{x}, t)C_{\mathsf{B}}(\mathbf{x}, t) + G_{\mathsf{B}}(\mathbf{x}, t),\end{aligned} \tag{6}$$

where $G_i(\mathbf{x}, t) = \sum_{t_i \in \mathcal{T}_i} N_i\delta(\mathbf{x}, t - t_i)$, ($\delta(\mathbf{x}, t - t_i)$ is Dirac delta function) and D_i denotes the diffusion coefficient for $i \in \{\mathsf{A}, \mathsf{B}\}$. In [7] and [8], this simplified model has shown to be in good agreement with the stochastic model in [11].

The mean $\overline{y}_i(t)$ in (5) is obtained by integrating $C_i(\mathbf{x}, t)$ via solving the system in (6). This can achieved by solving $C_i(\mathbf{x}, t)$ iteratively as proposed in [7] when the coexisting system does not absorb information molecules, and generic PDE solvers in the general case.

At time $t = kT,\ k = 1, \ldots$, the receiver makes a decision by sampling the number of molecules of Type-A and applying the threshold test

$$\hat{s}[k] = \left\{ \begin{array}{ll} 1, & y_{\mathsf{A}}(kt_s) \geq \gamma \\ 0, & \text{otherwise.} \end{array} \right\} \tag{7}$$

In particular, the average bit error rate induced by (7) is given by

$$P_e = \frac{1}{K}\sum_{k=0}^{K-1} \mathbb{P}(s[k] \neq \hat{s}[k]), \tag{8}$$

and γ is chosen to minimize the average probability of error for the whole sequence $s[0], \ldots, s[K-1]$. Note that by Corollary 1 in [8] the test in (7) corresponds to the maximum likelihood decision rule for symbol k, under the assumption that the past transmitted symbols forming the ISI are perfectly known.

A. Coexistence Constraints

In a crowded biochemical environment, it is necessary to account for the impact communication may have on external biological systems. For example, in [12] magnetic nanoparticles are proposed as information carriers. Although they are used in many biomedical applications, in sufficiently high concentrations there is the potential for such nanoparticles to cause cellular damage [13]. Another example is when Ca^{2+} molecules are used as information carriers [14]. In this case, the Ca^{2+} molecules can interfere with the structure of the lipid bilayer, compromising the membrane of a cell [15].

In order to account for undesirable interactions between information-carrying molecules and nearby biological systems, we introduce a coexistence constraint [2] [3]. In this paper, we desire that the communication system does not significantly change the expected total number of molecules that pass through the domain of an external biological system—with domain $\mathcal{V}^{\mathrm{Bio}}$—during the entire transmission of K bits. Formally, the coexistence constraint is given by

$$K_i = \mathbb{E}_{s[1],\ldots,s[K-1]}[Z_i] < \delta_i,\ i \in \{\mathsf{A}, \mathsf{B}\}, \tag{9}$$

where $Z_i = \int_0^{Kt_s} \overline{b}_i(t)\mathrm{d}t$ and $\overline{b}_i(t) = \int_{\mathbf{x} \in \mathcal{V}^{\mathrm{Bio}}} C_i(\mathbf{x}, t)\mathrm{d}\mathbf{x},\ i \in \{\mathsf{A}, \mathsf{B}\}$. Note that $\overline{b}_i(t)$ depends on the transmitted sequence via $G_i(\mathbf{x}, t)$ in (6).

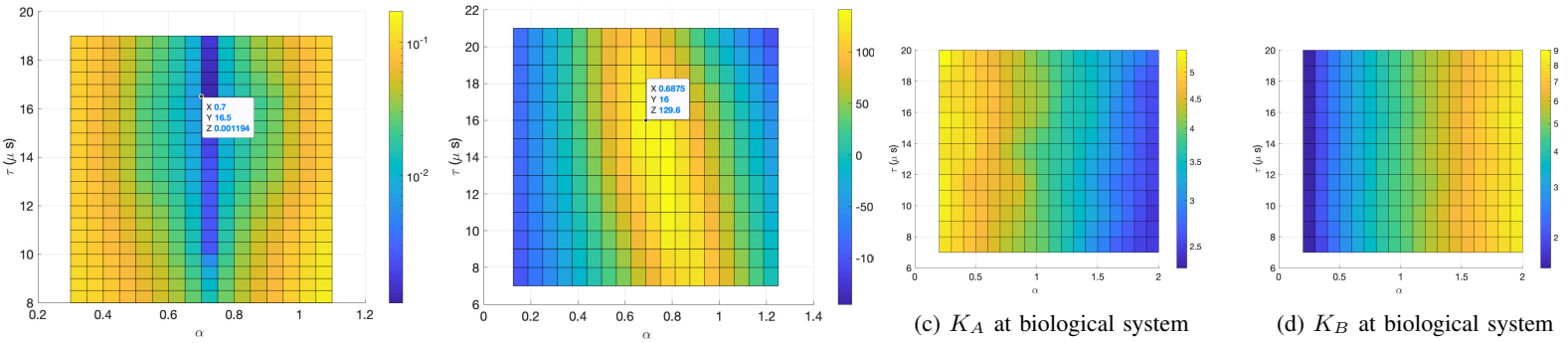
III. Optimizing the Reactive Signaling Scheme

In this section, we turn to the problem of optimizing the quantity and time of release for Type-B molecules in order to minimize the probability of error subject to the coexistence constraint in (9). In order to select the quantity of molecules of Type-B, α, and the time of release, τ, it is necessary to solve the optimization problem

$$\begin{aligned}\min_{\alpha,\tau} \quad & P_e(\alpha, \tau) \\ \text{subject to} \quad & 0 \leq \alpha \leq \alpha_{\max} \\ & 0 \leq \tau \leq t_s \\ & K_i(\alpha, \tau) \leq \delta_i,\ i \in \{\mathsf{A}, \mathsf{B}\},\end{aligned} \tag{10}$$

where the probability of error P_e is given in (8) and the coexistence constraints K_i are defined in (9). For comparison, earlier studies of reactive signaling, [7] and [8] have used reactive signaling for ISI reduction by choosing the quantity of Type-B molecules same as the quantity of Type-A molecules and time of release as the peak time of Type-A molecules.

The key difficulty in solving the optimization problem in (10) is that under the proposed communication scheme and system model, to the best of our knowledge, there is not any tractable formula for P_e in the literature. While it is possible to use the brute force approach to find good parameter choices, it requires extensive Monte Carlo simulations. An alternative approach is to use more sophisticated stochastic optimization methods. However, this approach still requires a number of



(a) P_e of the communication system

(b) SID values at the receiver

(c) K_A at biological system

(d) K_B at biological system

Fig. 1: P_e, $mSID$, K_A and K_B values of the system for $N_A = 5000$, $d = 250nm$, $D_A = D_B = 10^{-9}m^2s^{-1}$ $r = 50nm$, $t_s = 20\mu s$ and $\kappa = 10^{-17}molecule^{-1}m^3s^{-1}$. The labeled point corresponds to the optimal solution.

Monte Carlo samples. A key question is therefore whether a lower complexity, yet near optimal solution method exists. This question is addressed in the following section.

A. Modified SID Optimization Problem

In [16] and [17], the signal-to-interference difference (SID) was proposed to reduce inter-symbol interference interference (ISI) in diffusion-based molecular communication systems. In particular, the SID is the difference between the signal power and the interference power and it has been shown to be a good proxy for minimizing the probability of error in the presence of ISI.

A similar approach is also applicable for the reactive signaling scheme. Since both molecules of Type-A and Type-B are present in the channel, it is desirable to equalize the number of Type-A and Type-B molecules in order to balance the upcoming reactions for the next symbol intervals. In other words, when the number of remaining Type-A and Type-B molecules after the transmission interval are close to each other, there is less likely to be significant interference for future transmissions. Based on this intuition, a natural modification of the SID tailored to reactive signaling, called the *modified signal-to-interference difference (mSID)*, can be written as

$$mSID(\alpha,\tau) = \overline{y}^*_A(t_s) - \sum_{m=2}^{L} \left(|\overline{y}^*_A\left(mt_s\right) - \overline{y}^*_B\left(mt_s\right)|\right), \tag{11}$$

where $\overline{y}^*_A(mt_s)$ and $\overline{y}^*_B(mt_s)$ correspond to $\overline{y}_i(t)$ obtained from (5) and (6) when the transmitted sequence is all zero except the first element. As such, $\overline{y}^*_A(mt_s)$ and $\overline{y}^*_B(mt_s)$ are obtained taking $G_A(\mathbf{x},t) = N_A\delta_{\mathrm{d}}(\mathbf{x},t)$ and $G_A(\mathbf{x},t) = \alpha N_A\delta_{\mathrm{d}}(\mathbf{x},t-\tau)$. Note that the signal at time mt_s is due to intersymbol interference from the one shot transmission. We highlight that due to the fact that a one-shot transmission is used to compute the $mSID$, the evolution of the system is governed by (6) with initial conditions governed by the single transmission. The $mSID$ can then be computed by numerically solving (6), a single time.

The optimization problem in (10) can be approximated by

$$\begin{aligned} \max_{\alpha,\tau} \quad & mSID(\alpha,\tau) \\ \text{subject to} \quad & 0 \le \alpha \le \alpha_{\max} \\ & 0 \le \tau \le t_s \\ & K_i(\alpha,\tau) \le \delta_i,\ i \in \{\mathsf{A},\mathsf{B}\}. \end{aligned} \tag{12}$$

The general procedure for solving (12) is to first define the objective nonlinear objective function and constraints of the problem in (12). The mSID can then be optimized using standard methods from constrained nonlinear programming.

Therefore, a key feature of this approach based on the $mSID$ is that no Monte Carlo simulations are required. For a comparison of complexities of $mSID$ and P_e, let $O(c)$ be the required number operations to obtain the channel response due to any symbol $s[k]$. For the calculation of P_e, one needs to calculate the channel response of the whole transmitted randomly selected K-length sequence and repeat this procedure R times in order to estimate the probability of error, which requires a number of computations on the order of $O(NRc)$. On the other hand, for calculation of mSID, the only requirement is calculation of the response of $s[1]$ (i.e., setting $s[1] = 1$) which has complexity on the order of $O(c)$.

IV. Simulation Results and Discussion

In order to calculate P_e, Monte Carlo simulations are performed by transmitting realizations of different sequences whose lengths are $K = 50$. In order to obtain statistically meaningful results, $R = 10^3$ realizations of the sequences are used. In particular, assuming the channel memory is $L = 50$ the response of the channel for any particular sequence is first obtained by using (5). The probability of error is then calculated for the corresponding sequence as described in (7) and (8). To calculate the mSID, the only requirement is the calculation of (11), which is independent from the transmitted sequence.

To solve the optimization problem for P_e in (10), a brute force approach has been used. On the other hand, deterministic nonlinear programming is used for the proposed mSID-based approach. Although the simulations are conducted for various

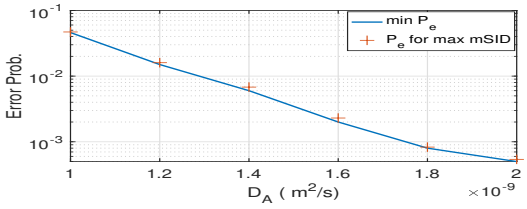
parameters, we present only one instance due to space constraints. The parameter set presented here is chosen to be the same as the parameter set used in [7], with results given in Fig. 1.

We remark that in [7] and [8], α and τ are chosen to be 1 and the peak time of the Type-A molecules, respectively. On the other hand, as can be seen in Fig. 1a, a local minimum can be found and it does not necessarily correspond to $\alpha = 1$. Furthermore, one can easily observe from Fig. 1a and 1b, that the solution minimizing P_e is very well approximated by the solution maximizing the $mSID$. As can be observed in Fig. 1c and 1d, as α increases, K_B increases and K_A decreases. This is expected since α is directly related to the amount of Type-B molecules in the environment and as the amount of Type-B increases, the number of reactions with Type-A molecules will also increase—leading to a decrease in the number of Type-A molecules.

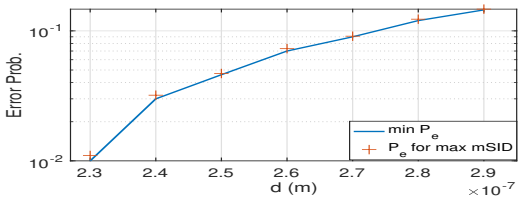
Also observe that K_A and K_B do not change significantly with τ. Therefore, it is possible to reduce the selection interval of α. In particular, the coexistence constraints can be satisfied by reducing the possible choices of α. Suppose that α_B is the value that satisfies $K_B = \delta_B$ and α_A is the value that satisfies $K_A = \delta_A$. Observe in Fig. 1c and Fig. 1d that if $\alpha_A > \alpha_B$, the solutions of the optimization problems in (10) and (12) are empty sets. For the other cases, the optimization problem in (12) can be simplified to

$$\max_{\substack{0<\tau<t_s \\ \alpha_A<\alpha<\alpha_B}} \quad mSID. \tag{13}$$

Depending on the coexistence constraints or constraints on the production of Type-B, it can also be possible that $\alpha_B = \alpha_A$, which implies that the minimization of P_e (or maximization of $mSID$) only requires the optimization of τ. Fig. 2 corresponds to this scenario, with the optimal τ based on P_e and the mSID for varying values of the diffusion coefficient D_A and distance d. As can be seen in Fig. 2, both P_e and the mSID yield quite similar results. This is also consistent with the results in Fig. 1a and 1b.



(a) for different D_A.



(b) for different d.

Fig. 2: Comparison of minimum P_e with brute force approach and P_e obtained by using $mSID$.

V. Conclusion

Reactive signaling was originally proposed to reduce inter-symbol interference in molecular communications. In this paper, we have shown that reactive signaling can also provide a means of satisfying coexistence constraints, where the impact on an external biochemical system is limited. A key challenge—both with and without coexistence constraints—is that time-consuming Monte Carlo approaches are required for parameter optimization. We have shown that an alternative objective, the mSID, can be used instead of the error probability. This allows standard deterministic optimization methods to be used, which significantly reduces the required computation to obtain near-optimal solutions.

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